PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference P045074PCT SMO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 03/00168	International filing date *(day/month/year)* 06.03.2003	Priority date *(day/month/year)* 12.04.2002
International Patent Classification (IPC) or both national classification and IPC B01J2/04		
Applicant FEYECON DEVELOPMENT & IMPLEMENTATION B.V. et Al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.10.2003	05.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Cubas Alcaraz, J Telephone No. +49 30 25901-324

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00168

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-14 received on 24.05.2004 with letter of 24.05.2004

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-9
	No:	Claims	1,10-14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

1. The following document is referred to:

D1: WO-A-00/37169
D2: WO-A-98/36825

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

2.1 Document D1 discloses a process for the preparation of particles by mixing a solution of the substance of interest with a supercritical fluid to extract the vehicle and to cause precipitation of the solved product (cf. page 1, lines 1-4; page 2, line 25-page 3, line 20; page 5, lines 4-5; Example 1). The mixing step is performed ensuring an improved dispersion of the solution containting the substance to be granulated, achieved by contacting the fluids having high fluid velocity. The mixture is fed to a tube (reference 17 in figure 1), similar to the tube of Example 1 of the present application wherein step b) takes place, thus it can be assumed that formation of very fine particle occurs inside the tube of figures 1 or 2 of D1. The particles are fed to a particle formation (growing) chamber (reference 19 in Example 1). Additional antisolvent is admixed in the tube wherein nucleation starts (cf. page 5, lines 19-26; example 2). The particles are finally collected.

2.2 Document D1 is silent with respect to the size of the particles prepared. However, it is noted that the size of the particles is the result of the process and not a feature of the process. In other words: having the process described in D1 all the features of the process disclosed in claim 1, it can be assumed that the size of the particles will fall into the range mentioned in claim 1, which, on the other hand, is the range of particle size normal in this kind of processes using supercritical fluid extraction. Accordingly, the subject-matter of claim 1 is not new regarding the disclosure of document D1 .

3. Dependent claims 2-14 do not appear to contain any additional features which in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty or inventive step (Article 33 PCT). These claims relate to parameters already disclosed in the prior art (as for claims 10-14), or parameters not giving rise to an unexpected technical effect, being the matter of an arbritary selection (claim 2-7).

3.1 Special reference is made to claims 8 and 9. The prior art is silent with respect to the cinetic energy applied in the mixing zone and mixing time. However, document D2, describing a similar process wherein mixing between supercritical fluid and a solution takes place, clearly specified that the cinetic energy of the fluids in the mixing zone has to be high (cf. page 3, line 15-page 4, line 2)). Since D2 does not mention the value of the energy, but the conditions of the examples of the present application, specialIly pressure of the fluids, are similar to the conditions in D2 (example 4), it can be assumed that both, energy applied to the mixing zone and mixing time, in the process disclosed in D2 have to fall into the ranges disclosed in claims 8 and 9 of the application. It would be obvious for the skilled person to use similar conditions in the process of D1. The subject-matter of claims 8 and 9 cannot be considered as involving an inventive step (Article 33 PCT).

CLAIMS

1. A process for the preparation of small particles through precipitation, which process employs a fluid solution comprising a solvent and solute to be precipitated and a non-gaseous antisolvent, said solvent being soluble in or miscible with the antisolvent and said solute being substantially insoluble in the antisolvent, wherein the process comprises the successive steps of:
   a. feeding a stream of the fluid solution and a stream of the antisolvent into a mixing zone where both streams are thoroughly mixed to achieve a condition of super saturation whilst ensuring that hardly any nucleation occurs during the mixing;
   b. feeding the resulting mixture of the fluid solution and the antisolvent into a nucleation zone allowing nucleation to commence;
   c. allowing the nuclei formed in the nucleation zone to grow to particles with a volume weighted average diameter of no more than 50 μm, preferably of no more than 7 μm.
   d. collecting the particles and separating them from the antisolvent.

2. The process according to claim 1, wherein during or following step b., and prior to step d. additional antisolvent is admixed to the mixture of the fluid solution and the antisolvent.

3. The process according to claim 2, wherein the additional antisolvent is admixed after the precipitated particles have grown to a volume weighted average diameter of at least 0.1 μm, preferably of at least of at least 0.4 μm

4. The process according to claim 2 or 3, wherein the antisolvent is admixed at least 1 second after completion of step a., preferably at least 3 seconds after completion of step a.

5. The process according to any one of claims 1-4, wherein the ratio of the solution flow rate to antisolvent flow rate in step a. is between 5:1 and 1:10.

6. The process according to any one of claims 1-5, wherein the collected particles, when reaching the end of the nucleation zone or immediately prior to the admixture of additional antisolvent, contain at least 1 wt.% solvent, preferably at least 10 wt.% solvent.

7. The process according to any one of claim 2-6, wherein the additional antisolvent is admixed in an amount effective to reduce the solvent content of the collected particles to less than 1 wt.%, preferably to less than 0.01 wt.%.

8. The process according to any one of claims 1-7, wherein less than 25%, preferably less than 10% of the nuclei formed in the process are formed in the mixing zone.

9. The process according to any one of claims 1-8, wherein the residence time within the mixing zone is less than 15 seconds, preferably less than 1 second.

10. The process according to any one of claims 1-9, wherein the mixing energy applied in the mixing zone exceeds 1 J/kg and preferable more than 10J/kg.

11. The process according to any one of claims 1-12, wherein the residence time within the nucleation and growth zone is at least 3 seconds, preferably at least 60 seconds.

12. The process according to any one of claims 1-11, wherein the solution comprises between 0.0001 and 30 wt.%, preferably between 0.1 and 5 wt.% of the solute.

13. The process according to any one of claims 1-12, wherein the antisolvent is a supercritical or nearcritical fluid.

14. The process according to any one of claims 1-13, wherein the particles obtained from step c. have a particle size distribution with a standard deviation of less than 50% of the volume weighted average particle size, preferably of less than 20% of the volume weighted average particle size.

15. The process according to any one of claims 1-14, wherein at least 10 wt.%, preferably at least 50 wt.% of the solute present in the stream of the fluid solution of step a. is recovered in the particles obtained in step d.